IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Pastan et al.
Application No. 09/763,393
Filed: July 30, 2001
Confirmation No. 5265
For: PAGE-4, AN X-LINKED GAGE-LIKE GENE EXPRESSED IN NORMAL AND NEOPLASTIC PROSTATE, TESTIS AND UTERUS, AND USES THEREFOR
Examiner: Minh-Tam Davis
Art Unit: 1642
Attorney Reference No. 4239-61541-01

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Date Mailed May 15, 2007

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TRANSMITTAL LETTER

Enclosed for filing in the application referenced above are the following:

☒ REPLY TO EXAMINER'S ANSWER

☒ The Director is hereby authorized to charge any additional fees that may be required, or credit over-payment, to Deposit Account No. 02-4550. A copy of this sheet is enclosed.

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Respectfully submitted,

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REPLY TO EXAMINER'S ANSWER

This responds to the Examiner's Answer dated March 21, 2007. A two-month period was set for response, making this reply due May 21, 2007.

Grounds of Rejection to be Reviewed on Appeal and Withdrawn Rejection

Claims 1-2, 4, 6-8, 14-15, 17-18 and 53-57 stand rejected under 35 U.S.C. § 101 as allegedly there is no utility for the claimed subject matter. Claims 1-2, 4, 6-8, 14-15, 17-18 and 53-57 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not being enabled by the specification.

The Examiner has withdrawn the written description rejection of claims 1-2, 4, 6-8, 14-15, 17-18 and 54-57 under 35 U.S.C. § 112, first paragraph. Thus, there is sufficient written description for the claimed subject matter.

The utility and enablement rejections are the sole remaining grounds for rejection.

Rejection Under 35 U.S.C. § 101 (Utility)

The Examiner's Answer alleges that there is no specific, well-established utility for claims 1-2, 4, 6-8, 14-15, 17-17 and 53-57. However, the specification describes that the claimed polypeptides can be used to produce antibodies (see the specification, page 25, line 11 to page 27 , line 9) that can be conjugated to detectable labels (see the specification, page 31, line 27 to page 32, line 9). The Examiner's Answer alleges that because differential expression of PAGE4 in prostate cancer has not been demonstrated, and because the Applicants have only shown expression of PAGE4 mRNA in prostate cancer (and not protein), that there simply can be no use for the claimed polypeptides. This is incorrect.

Cancer is known to metastasize; prostate cancer metastasizes to bones, lymph nodes, rectum and bladder (see Wikipedia on the internet). It is well known that the origin of a cancer can provide substantial insight into treatment methods. Thus, expression of a polypeptide encoding SEQ ID NO: 1 can be used to identify a tumor in a bone, lymph node, rectum or bladder as being of prostate or uterine origin. Indeed, the specification describes that antibodies to PAGE4 can be used to detect PAGE4 (SEQ ID NO: 1) expressing cells, to determine whether metastatic cells of a prostate cancer (or another PAGE4 expressing cancer) have "invaded other parts of the body" (see the specification at page 6, lines 20-24). The Examiner's Answer acknowledges that peptides from SEQ ID NO: 1 can be used to generate antibodies. Indeed, the specification discloses the production of polyclonal antibodies to a fragment of SEQ ID NO: 1 (see Example 3, page 41 of the specification).

Antibodies are also routinely used in histological analysis, and are often sold as parts of a kit for the detection of PAGE4-expressing cells in any biological sample (see the specification at page 38, line 35 to page 39, line 9). The antibodies disclosed herein could be used in routine histological analysis, such as to determine the presence of prostate or uterine cells in a sample. Thus, there is a credible, specific, and substantial utility for the claimed polypeptides in the production of antibodies for the detection of specific cell types in tissue samples as well as for the detection of metastasis.

The Examiner's Answer seems to allege that there can be no use for PAGE4 polypeptides, or fragments thereof, because the expression of mRNA encoding PAGE4 and PAGE4 protein levels simply could not be related. This is contrary to what is asserted in the specification, and indeed, the Declaration of Dr. Pastan presents confirmatory studies that have

shown the presence of mRNA in the absence of protein for other (completely unrelated) genes. The data presented in the specification (see Fig. 2B, Fig. 4, and Table 1) document expression of the polynucleotide in normal prostate, prostate cancer, uterus and uterine cancer. In addition, the Declaration of Dr. Pastan and the Iavrone et al. reference (Mol. Cancer Therap. 1: 329-335, 2002, of record) describes an analysis (Western blot) that confirmed that PAGE4 protein (SEQ ID NO: 1) was expressed in a prostate cancer lysate (see also Fig. 2B of Iavrone et al., for an exemplary blot).[1] *For PAGE 4, there was a 100% correlation between mRNA expression and protein expression. In addition, the studies confirmed that PAGE4 is expressed in prostate cancer.* Thus, PAGE4 polypeptides are clearly of use for the detection of prostate cancer; the references cited by the Examiner are simply not relevant to PAGE4.

The Examiner's Answer alleges that there can be no utility for the claimed polypeptides in the detection of cancer simply because the data in the specification shows expression of PAGE4 in normal prostate tissue, at a similar level to prostate cancer that is "barely detectable" (see page 6, point A of the Examiner's Answer). However, the allegation that PAGE4 is "barely detectable" is clearly incorrect, as there are additional results presented in Table 1 of the specification and in the Declaration of Dr. Pastan that document that PAGE4 (SEQ ID NO: 1) is clearly detectable in prostate cancer. In addition, the expression of a protein by normal tissue does not negate the utility of the protein for cancer treatment. For example, total resection of an organ, such as the uterus, can used for the treatment of a cancer. The theory behind total resection is that removal of normal tissue negates the possibility that this tissue will become cancerous. Thus, the removal of residual normal tissue expressing PAGE4 may, in some instances, be considered advantageous.

The Examiner's Answer further asserts that because cancer immunotherapy is unpredictable, there can be no utility for the claimed polypeptides (see page 9 of the Examiner's Answer, part B). The Examiner's Answer agrees that it has been demonstrated that a polypeptide of 8 to 11 amino acids of SEQ ID NO: 1 can be used to activate human cytotoxic T cells, and that these human cytotoxic T cells were demonstrated to lyse human prostate cancer

[1] The Examiner's Answer alleges that the data presented in Iavrone et al. relate to a different protein than SEQ ID NO: 1 because the protein is highly expressed in normal prostate and prostate cancer (and alleges that while Fig. 4 shows low expression). Dr. Pastan has confirmed under oath that the data presented in Iavrone et al. studies the same polypeptide. Thus, it is inappropriate for the Examiner to assert that the proteins are unrelated. The apparent

cells *in vitro*. However, the Examiner's Answer cites a number of references which describe difficulties in using cancer vaccines, and assets that these references demonstrate the lack of utility for any polypeptide that can be used for cancer therapy. The Examiner's Answer asserts that data in patients must be presented in order to substantiate any utility for treating cancer. Applicants respectfully disagree with these assertions.

The core of the present rejection appears to be based on the absence of human clinical data. Extensive pre-clinical in vivo data is required by the Food and Drug administration prior to testing in humans. Human clinical data is clearly not the only means of establishing utility (In re Krepelka, 231 USPQ 746 (Bd. Pat. App. & Inter. 1986)). In taking the position that the only acceptable proof of utility would be human clinical trial data the Patent Office is failing to recognize *in vitro* data, and possibly thwarting a therapy that could benefit patients.

In addition, showing of a failure of one particular therapy for the treatment of cancer, or a showing of difficulties in designing treatment, does not negate an asserted therapeutic use for alternative therapies. The Applicants only need to document a reasonable correlation between the activity and the asserted use. Clearly, the ability to generate human cytotoxic T cells (CTLs) that kill autologous human prostate cancer cells *in vitro*, documents that the claimed polypeptides could be used for treatment of prostate cancer.

The negative statements made in the final Office action specifically contradict MPEP § 2107, which confirms that even in situations where there are no previously successful treatments (and this most certainly is not the case with prostate cancer), there is no basis for a rejection on the basis of utility. MPEP § 2107 describes that prior to the 1980's, there were a number of cases where an asserted use in treating cancer in humans was viewed as "incredible." *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Buting*, 418 F.2d 540, 163 USPQ 689 (CCPA 1969); *Ex parte Stevens*, 16 USPQ2d 1379 (Bd. Pat. App. & Inter. 1990); *Ex parte Busse*, 1 USPQ2d 1908 (Bd. Pat. App. & Inter. 1986); *Ex parte Krepelka*, 231 USPQ 746 (Bd. Pat. App. & Inter. 1986); *Ex parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981). Only in those cases where the applicant was unable to come forward with any relevant evidence to rebut a finding by the Office that the claimed invention was inoperative was a 35 U.S.C. § 101 rejection affirmed by the Court (*In re Buting*, 418 F.2d 540, 543, 163 USPQ 689, 690 (CCPA

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increased expression in Ivarone et al. is related to the sensitivity of the assay used. The results actually buttress the results presented in the specification.

1969); record did not establish a credible basis for the assertion that the single class of compounds in question would be useful in treating disparate types of cancers). In all of the other cases the treatment of cancer was viewed to be a specific, substantial and credible use. In the present case, the record contains relevant evidence to rebut the finding by the Office of inoperability. Thus, the rejection under 35 U.S.C. § 101 should be withdrawn on this basis alone.

In view of the above remarks, the Applicants believe it is inappropriate for the Office to maintain the rejection under 35 U.S.C. § 101. Only a single utility need be present to overcome the § 101 rejection. The Applicant has shown that the claimed polypeptides are useful either in the detection of prostate tissue (including metastatic tumors) or treatment of prostate cancer. The utility rejection should be reversed.

Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner's Answer maintains the rejection of the pending claims under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification. The Examiners Answer asserts that all of the claims are broad, and raises several general issues about the invention (see the Examiner's Answer, page 32). However, the issues are not directed to specific sets of claims, with the exception, perhaps, of the method claims. The below response has attempted to address the remaining issues as framed by the Examiner.

a) *There is no information in the specification, nor could one predict, that there would be any other use for a polypeptide with an amino acid sequence set forth as SEQ ID NO: 1, other than detecting or treating cancer, which is not a viable use.* The Examiner's Answer acknowledges that the claimed polypeptides can be routinely synthesized or made recombinantly (see page 32, paragraph a). As discussed above, the claimed polypeptides can be used to produce antibodies; the specification describes that these antibodies can be used for the detection of cells in standard histological analysis. Moreover, the specification discloses that the antibodies can be used to determine if a metastatic cancer is of prostate or uterine origin. Furthermore, ample evidence has been submitted documenting that the claimed polypeptides can

be used to detect and treat cancer (see above). Thus, any rejection on this basis is inappropriate, as discussed above. The method claims are therefore enabled.

(b) One can not predict which of the nine amino acids that bind to MHC and could induce cytotoxic T cell (CTL) lysis. The Examiner's Answer acknowledges (1) that there are computer programs that exist that will predict which fragments of SEQ ID NO: 1 will bind MHC (see the Examiner's Answer, page 32, paragraph b), (2) that there are well known methods to synthesize the claimed polypeptides (see above), and (3) that the level of skill in the art is high (see the Examiner's Answer, page 33, first paragraph). Thus, these elements are not in dispute. However, the Examiner's Answer alleges that it cannot be known which polypeptides that bind MHC will activate CTLs, and thus that the immunogenicity of the claimed polypeptides is unpredictable (see page 32)[2] Applicants assume that these statements are directed to claims 14-15 and 17-18, which are directed to methods of treatment.

Again, the Examiner relies on data obtained with unrelated polypeptides to support the unpredictability of the claimed peptides and methods, even in the face of a detailed specification supporting the claimed uses, and further in view of data documenting the reduction to practice of the claimed peptides and methods. The specification describes biological methods that can be used to test whether a specific polypeptide fragment of PAGE4 (SEQ ID NO: 1) is immunogenic (for example, see page 8, lines 1-4 and page 21, lines 3-12 and lines 20-29). The Declaration of Dr. Pastan documents the production of the claimed polypeptide fragments and the use of a polypeptide fragment to bind MHC and activate CTLs (which in turn were shown to specifically lyse prostate cancer cells). All of the studies presented in the Declaration of Dr. Pastan were performed using the guidance and methods disclosed in the specification. Clearly it has been documented that one of skill in the art could readily produce polypeptides of 8 to 11 amino acids in length that bind MHC, use these peptides activate CTLs, and use the CTLs to lyse cancer cells without undue experimentation.

[2] Page 32 of the Examiner's Answer acknowledges that "the use of some immunogenic peptides to inhibit growth of malignant cell is well known in the art..."

(c) *There are no data in the specification or in the art showing that PAGE4 (SEQ ID NO: 1) or any of its fragments that bind MHC could successfully be used to inhibit the growth of malignant cells, in view of the teachings in the prior art.*

Immunogenic peptides are clearly described in the specification (see page 7, line 35 to page 8, line 25, and on page 20, line 1 to page 22, line 5), including specific configurations of use such as wherein the PAGE4 polypeptide is 9 or 10 amino acids in length and includes binding motifs for HLA-A2 or have specified anchoring residues (see, for example, page 8, lines 30-37, page 20, to page 21, line 2; page 21, lines 15-19; page 20, line 20 to page 21, line 2; and page 28, line 25 to page 29, line 29). Biological methods of testing whether a specific epitope is immunogenic are also provided in the specification (see page 8, lines 1-4 and page 21, lines 3-12 and lines 20-29). Moreover, the inventors have provided documentation in the Declaration of Dr. Pastan that, using the guidance provided by the specification and methods that are admittedly known in the art, polypeptides of 8 to 11 amino acids in length of SEQ ID NO: 1 were produced that bind MHC. One polypeptide was selected for more extensive studies. This polypeptide was successfully used to activate human CTLs, and were shown to lyse human prostate cancer cells in an in vitro assay.

Thus, the claimed polypeptides can be produced using methods acknowledged to be routine in the art, can be used to produce antibodies, and work in an art-recognized *in vitro* model of prostate tumor cell lysis. Thus, there claimed polypeptides are clearly enabled by the specification. The allegation that there is no data supporting the use of the claimed polypeptides to inhibit the growth of (or kill) malignant cells is incorrect. A working example has been provided, as discussed above. Thus, the claimed peptides and claimed methods are all fully supported by the specification.

Conclusion

Applicants submit that the rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph should be reversed, and respectfully request the allowance of the pending claims.

Respectfully submitted,

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